DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Mary Kay Delmedico, Ph.D.
Director, Drug Development & Portfolio Management
DaraBiosciences, Inc.
8601 Six Forks Road, Suite 160
Raleigh, NC 27615

RE: NDA 021807
Soltamox® (tamoxifen citrate) oral solution
MA# 21

Dear Dr. Delmedico,

The Office of Prescription Drug Promotion (OPDP) of the Food and Drug Administration (FDA) has reviewed a sales aid (SA21112) for Soltamox® (tamoxifen citrate) oral solution (Soltamox) submitted by DaraBiosciences, Inc. (DaraBiosciences) under cover of Form FDA 2253. The sales aid is misleading because it omits material facts, contains unsubstantiated superiority claims, and omits important risk information for Soltamox. Thus, the sales aid misbrands the drug within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and makes its distribution violative of the FD&C Act, 21 U.S.C. 352(a); 321(n); 331(a), and implementing regulation 21 CFR 1.21(a). *Cf.* 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(ii); (e)(7)(i).

Background[1]

Below are the indications and summary of the most serious and most common risks associated with the use of Soltamox. According to the INDICATIONS AND USAGE section of the FDA-approved Soltamox product labeling (PI) (in pertinent part):

Metastatic Breast Cancer: Tamoxifen citrate is effective in the treatment of metastatic breast cancer in women and men. . . . Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from tamoxifen citrate therapy.

Adjuvant Treatment of Breast Cancer: Tamoxifen citrate is indicated for the treatment of

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional pieces cited in this letter.

node-positive breast cancer in postmenopausal women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. . . .

Tamoxifen citrate is indicated for the treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation.

The estrogen and progesterone receptor values may help to predict whether adjuvant tamoxifen citrate therapy is likely to be beneficial. . . .

Ductal Carcinoma in Situ (DCIS): In women with DCIS, following breast surgery and radiation, tamoxifen citrate is indicated to reduce the risk of invasive breast cancer. . . .

Reduction in Breast Cancer Incidence in High Risk Women: Tamoxifen citrate is indicated to reduce the incidence of breast cancer in women at high risk for breast cancer. . . .

Soltamox is associated with a number of serious risks, some of which have been fatal, including a Boxed Warning for uterine malignancies, stroke, and pulmonary embolism in women with DCIS and women at high risk for breast cancer. Soltamox is contraindicated in patients with known hypersensitivity to the drug or any of its ingredients, in women who require concomitant coumarin-type anticoagulant therapy, and in women with a history of deep vein thrombosis or pulmonary embolus. The PI also contains Warnings regarding hypercalcemia in metastatic breast cancer patients; effects on the uterus (endometrial cancer and uterine sarcoma); non-malignant effects on the uterus; thromboembolic effects; liver cancer; non-malignant effects on the liver; other cancers; effects on the eye; and fetal harm. In addition, the PI includes Precautions regarding myelosuppression; monitoring during Soltamox therapy; drug interactions; drug/laboratory interactions; fertility impairment; and lactation inhibition.

The most common adverse events observed with Soltamox include hot flashes, flush, fluid retention, vaginal discharge, nausea, irregular menses, weight loss, vasodilation, and vaginal bleeding.

Omission of Material Facts

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. Page two of the sales aid states (bolded emphasis original, underlined emphasis added):

> **DOSAGE AND ADMINISTRATION**
>
> <u>For patients with breast cancer</u>, the recommended daily dose is 20-40 mg. Dosages greater than 20 mg per day should be given in divided doses (morning and evening). A 20 mg dose of SOLTAMOX is administered as 10 mL (equivalent to 2 teaspoons) of the oral solution.

Although this statement is taken directly from the Dosage and Administration section of the approved PI, it makes a representation about the use of Soltamox in the treatment of breast cancer. However, this promotional piece fails to include the full approved indications for Soltamox. Specifically, as provided above, the INDICATIONS AND USAGE section of the Soltamox PI describes the use of this product for the treatment of patients with metastatic breast cancer, the adjuvant treatment of node-positive and node-negative breast cancer, the treatment of ductal carcinoma in-situ, and reducing the incidence of breast cancer in women at high risk for breast cancer. However, the sales aid fails to include this material information.

Unsubstantiated Superiority Claims

Promotional materials are false or misleading if they represent or suggest that a drug is safer or more effective than another drug, when such has not been demonstrated by substantial evidence or substantial clinical experience. Specifically, the sales aid includes the following claims (bolded emphasis original):

> ## CHALLENGE
>
> **Compliance and adherence** to prescribed tamoxifen therapy is a critical issue in patient care and may affect treatment outcomes.[2],[3]
>
> **Difficulty swallowing pills** may affect both compliance and adherence to prescribed courses of oral solid medications.
>
> ## SOLUTION
>
> **Liquid medication may be preferred vs. pills by many patients**
>
> - Many adults in the USA were reported to have experienced difficulties with swallowing tablets or capsules at some point, even though most had no problems swallowing food or liquid
> - Research shows that women experience more discomfort with pill swallowing compared to men
> - Many adults who have trouble ingesting their medication have not discussed the situation with a health professional
>
> **Soltomox** [sic], **the only tamoxifen citrate oral solution that may support long-term adherence**
>
> - For many reasons patients may have difficulty swallowing their medication.

[2] Owusu C, Buist DS, Field TS, et al. Predictors of tamoxifen discontinuation amoung [sic] older women with estrogen receptor-positive breast cancer. *J Clin Oncol*. 2008;26:549-555.
[3] Lash TL, Fox MP, Westrup JL, Fink AK, Sillman RA. Adherence to tamoxifen over the five-year course. *Breast Cancer Res Treat*. 2006;99:215-220.

- Responding to **patient preference** for liquid medication may provide an opportunity to increase compliance and adherence to prescribed medical therapy.

- Convenient

The totality of these claims and presentations suggests that, as a result of its liquid dosage form, Soltamox offers a therapeutic advantage over other available formulations of tamoxifen, including a positive impact on long-term patient compliance, adherence to treatment, patient preference, convenience, and treatment outcomes. The first claim cited above references two articles that discuss predictors of tamoxifen discontinuation and non-adherence in women with breast cancer. These studies did not specifically evaluate the liquid formulation of tamoxifen (i.e., Soltamox) or its impact on compliance or adherence for women taking tamoxifen. Therefore, these references do not provide substantial evidence to support this claim in the context of Soltamox promotion. OPDP acknowledges that Soltamox is the only tamoxifen citrate oral solution available in the U.S. at this time. We also acknowledge that tablets or capsules may pose challenges in patients who may have difficulty swallowing. However, we are not aware of substantial evidence that demonstrates that the liquid formulation of Soltamox will improve patient compliance or adherence to any particular treatment regimen or have a positive impact on convenience, treatment outcomes, or patient preference for Soltamox. If you have evidence to support these claims, please submit it to FDA for review.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

The sales aid makes representations regarding the use of Soltamox, but omits important risk information for the product. Specifically, the back page of the sales aid presents information regarding the Boxed Warning, contraindications, and the serious risks of hypercalcemia and thromboembolic events, but omits the other warnings, precautions, and adverse reactions associated with Soltamox therapy (see Background). By omitting this important risk information, the sales aid misleadingly suggests that Soltamox is safer than has been demonstrated. We acknowledge the statement, “Please see accompanying package insert for full prescribing information” on the bottom of the back of the sales aid; however, this statement does not mitigate the misleading omission of important risk information in the sales aid.

Conclusion and Requested Action

For the reasons discussed above, the sales aid misbrands Soltamox within the meaning of the FD&C Act, and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a), and implementing regulation 21 CFR 1.21(a). *Cf.* 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(ii); (e)(7)(i).

OPDP requests that DaraBiosciences immediately cease misbranding Soltamox. Please submit a written response to this letter on or before January 7, 2014, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission

date) for Soltamox that contain presentations such as those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA# 21 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as Response to Untitled Letter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your distribution of Soltamox complies with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Marybeth Toscano, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion

Karen Rulli, Ph.D.
Team Leader
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARYBETH TOSCANO
12/20/2013

KAREN R RULLI
12/20/2013